



<http://intl.elsevierhealth.com/journals/ijid>

Addressing the concerns about smallpox[☆]

Jean Pascal Zanders^{*}

BioWeapons Prevention Project, Avenue de Sécheron 12, Ch-1202, Geneva, Switzerland

Introduction

What is smallpox?

Smallpox (Variola) is an acute contagious viral disease that has a relatively high fatality rate in an immunologically naive population.

Smallpox is a member of the larger pox family of viruses.

Smallpox can manifest itself in two clinical forms: Variola major and Variola minor. Variola major in its common manifestation is more widely known as a consequence of the extensive rashes and pustules covering large parts of the body and the ugly lesions that mark the survivors for the remainder of their life. In 30 percent of cases the infection is fatal. However, there are two rare types of smallpox infection, namely malignant (or flat) and hemorrhagic smallpox, that are extremely severe and almost always fatal (mortality rates are 95–100 percent and 94 percent, respectively, in unvaccinated victims). In cases of malignant smallpox no pustules are formed, but the lesions remain soft and flat instead. Hemorrhagic smallpox is characterized by hemorrhage into the mucous membranes and the skin. There also exists a mild form of Variola major, which occurs in people who were previously vaccinated. The latter three types accounted for less than 10 percent of all cases. Variola minor, or alastrim, is rarer and its consequences less severe,

although it produced lesions similar to those of Variola major. Mortality averaged around one percent of infected people.

Smallpox can be transmitted from person to person after direct and fairly prolonged face-to-face contact, or through direct contact with bodily fluids of an infected person or contaminated bedding, clothing, or other fomites. (The virus can remain viable for about 1 week outside a human.) An infectious individual becomes most contagious with the onset of the rash, about 14–18 days after the infection, and remains contagious to others until the last scab has fallen off. However, the large amounts of virus shed from the skin are not very infectious, and the risk of transmitting the disease is consequently lower. A very high percentage of the survivors (65–80 percent) are scarred with pockmarks, while up to a third suffer permanent blindness.

Insects or other animal vectors do not play a role in the transmission of smallpox. There is no specific treatment of smallpox other than the management of symptoms. Vaccination was key to the preventive strategies until the eradication of smallpox was complete. It is nevertheless possible to vaccinate an infected person up to four days after exposure, resulting in immunity or arresting the severity of the disease.

How did smallpox affect civilization in the past?

Smallpox afflicted humankind for several thousands of years. It is believed to have originated about 3000

[☆] BioWeapons Prevention Project

^{*} Tel.: +41 22 908 5741; fax: +41 22 738 3582.

E-mail address: jpzanders@bwpp.org.

years ago in either India or Egypt. Because of its high mortality rate, smallpox epidemics impacted on the course of history. For example, Indian civilizations in the Americas collapsed following the arrival of European explorers and colonizers in the 16th century.

It is estimated that in the early 1950s there were 50 million cases of smallpox worldwide each year.

Was the smallpox eradication program successful?

Origins of vaccination: In 1798 Edward Jenner demonstrated that smallpox could be controlled through inoculation with the related cowpox virus. His technique replaced earlier efforts to inoculate people with the causative agent of smallpox itself, which carried a high risk of a fatal or mutilating infection.

Origins of WHO program

In 1967 the World Health Organization (WHO) launched an intensified smallpox eradication program under Donald H. Henderson.

Results

The last case of naturally occurring smallpox in the world was in Somalia in 1977; a case of fatal exposure to the virus happened in a British laboratory in 1978. A scientific commission concluded in December 1979 that smallpox had been globally eradicated and the World Health Assembly endorsed its findings in 1980.

Which countries possess the smallpox virus? Is it in the hands of terrorists?

Officially smallpox strains are in two WHO-designated repositories only, namely the WHO Collaborating Centre for Smallpox & Other Poxvirus Infections, Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia (USA) and the WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA, State Research Centre of Virology and Biotechnology 'Vector' in Koltsovo, Novosibirsk Region, Russian Federation.

The Soviet Union was said to have embarked on a major smallpox production program in the early 1980s (when the world was formally declared free from the disease). Even today, some US sources still accuse Russia of maintaining a facility capable of producing tonnes of the virus per year and supporting a research program into more virulent and contagious smallpox strains. Moreover, fear exists that even if the Russians closed down these programs, the expertise may have moved to other countries.

US smallpox proliferation claims are partly rooted in this fear.

The countries the United States lists with regard to its concerns over smallpox proliferation are the same ones it lists with regard to chemical and biological weapon (CBW) proliferation in general: Iran, Iraq, Libya, and North Korea. However, no conclusive evidence that the proliferation has actually taken place has been presented in public. Since the occupation of Iraq by US-led coalition forces in April 2003, evidence of Iraqi CBW stockpiles or a recent active CBW research and development program has proved elusive. (Nevertheless, in the 1990s UN inspection teams found evidence of Iraqi work on camelpox.) According to the Washington Post (5 November 2002), a US intelligence review also included France in the list of countries possessing undeclared stocks of the smallpox virus, using it to research defensive mechanisms in the case of an outbreak. France categorically denied the allegation, and said that it is conducting its research with authorized animal samples.

The intelligence review also indicated that the Al Qaeda terrorist network was interested in the virus.

What is today's smallpox threat?

The smallpox threat is defined to a large extent by the projection of past experiences into a future of new technological opportunities for the deliberate spread of disease; new security actors like terrorists and rogue states; and a global population that is increasingly immunologically naive as a consequence of the termination of mandatory vaccinations in the 1970s and 1980s. Threat warnings habitually emphasize the high case-fatality rates and transmissibility of the virus, characteristics that make them ideal candidates for bio-terrorism.

The assessment of the threat depends largely on what factors of disease propagation participants in the debate wish to emphasize. People who came down with Variola major were usually bedridden before the onset of rash (i.e., the most contagious phase) and remained so until the disease had run its course. As a consequence of the limitation on movement the number of people that could be infected through direct interaction with the patient was limited. (In contrast, the effects of Variola minor are less debilitating during the most contagious phase so that the infected individuals remained ambulatory and transmitted the disease over a much wider area.) This seems to limit the possibility of the disease spreading like wildfire or the likelihood of a self-infected suicide terrorist contaminating large numbers of people in crowded areas.

In the case of a smallpox outbreak, the emphasis must be on epidemic control. This means that in the case of deliberate release of the virus there will be a number of victims, including fatalities, before the outbreak can be contained. Besides the availability of vaccines, the presence of a developed and operational disease surveillance infrastructure is key to limiting the consequences of the outbreak. First, it will allow speedy detection of the outbreak, and second, trace the route of the outbreak in order to maximize the effectiveness of vaccination strategies and thus contribute (together with patient isolation) to the breaking of the transmission chain.

Some concern has been expressed that malignant research might try to elucidate the mechanisms that contribute to the development of hemorrhagic smallpox, as its mortality rates are much higher than the common form and the darkening of the skin and excretion of black fluids would maximize its terrorizing effect.

In the event of an outbreak today, what might happen?

Smallpox epidemics tended to develop relatively slowly with a 2–3 week interval between each generation. Furthermore, with natural outbreaks, an infected person would rarely transmit the virus to as many as five other individuals. However, the statistics collected during the WHO eradication program were based on observations of populations with immunity from vaccination or previous exposure. Some recent estimates suggest that on average up to ten people could be infected by a single source as a consequence of the receding immunity in the world's populations.

On the other hand, the ventilation systems in buildings allow the infection of individuals in removed or otherwise unconnected rooms, suggesting a vulnerability in the confined spaces of modern structures.

Can governments take useful measures to deal with the smallpox concerns?

Generic measures, which can also be applied in the remote eventuality of a smallpox outbreak, can deal with most aspects of the threat posed by biological (and chemical) terrorism. No government can prepare to deal with all contingencies, because the range of possibilities is bewilderingly wide. The measures to be taken in order to prevent acts of terrorism, protect the population and infrastructure, and deal with the consequences of a terrorist event must be designed and executed in such a way that they cause the least disruption to economic and

social activities and do not diminish the fundamental organizing principles of a society. While it is necessary for policy makers to sufficiently prioritize the threats posed by biological terrorism, it is equally important not to excessively dramatize the threat and especially the consequences of hypothetical events. A range of generic measures that bolster the existing health and emergency infrastructure and procedures may go a long way in dealing with such threats. Rather than disrupting the respective societies, they may actually be beneficial.

Among such measures are investments in the health infrastructure so that there is a good regional distribution of emergency wards and a spare capacity of beds. Furthermore, it may be sound policy to fund the establishment of an adequate number of specialized laboratories in geographically distributed hospitals for rapid identification of rare pathogens in order to be able to rapidly give first responders and other emergency personnel information about the nature of the infection. Annual refresher and training courses for doctors and other medical staff can be used to familiarize them with unusual diseases - including smallpox - in order to improve their ability for rapid and accurate diagnoses.

Other important investments are in areas of compatible communications technologies for the different emergency services and adequate field detection and diagnostic equipment for the civil emergency units, and the creation of sufficient supplies of medication and equipment. Recurring realistic exercises must be conducted in order to test and improve procedures and equipment.

Specific requirements include the stockpiling of vaccines and medication against biological warfare agents.

Before there is a serious incident - especially with a highly contagious pathogen - government authorities should identify the priority services and personnel who should have access to pretreatments and medication. These groups of people extend beyond the obvious categories of first responders, medical staff, and police forces. In the just-in-time economies of advanced industrialized states, personnel responsible for the energy supply, food distribution, and so on, are equally vital to prevent the collapse of a functioning society. Such an assessment should be based on the careful analysis of the functioning of critical infrastructure and integration of services in the EU member states.

Crisis communication strategies are designed to be able to inform the public in a responsible way. They form an integral part of the preparations described in the previous section. Among the measures to be considered are the identification of authoritative sources of information for the public

at the national and EU levels and the establishment of procedures to maintain communication even under the gravest of circumstances. Both the national and EU authorities should conclude agreements with different types of media in order to prevent as much as possible wrong or sensationalist reporting that might contribute to panic. In addition, political authorities and key personnel should receive training in crisis communication. The communication strategies at high-risk industrial facilities and industrial evacuation procedures probably offer a good starting point.

Simulation exercises and training in crisis response and management are required at all levels of decision making and across the multiple agencies that would be involved in a large-scale emergency. They must involve local, regional and national politicians, the people responsible for managing and overseeing emergency responses, and the press.

Tabletop exercises for the highest levels of decision makers focus on overall co-ordination and communication strategies with the different services and commanders on the scene of the incident. While single-day exercises suffice to test certain components of the emergency procedures, the need exists to plan occasional simulations that may last several days to examine the overall integration of these components. The tabletop exercises are complemented by realistic, multiple-day field exercises simulating the exercise on the ground. It is imperative that the simulations are carried through to their planned end, even if situations emerge that are unpalatable to democracies.

EU members are already conducting such simulations with regard to incidents at nuclear or industrial facilities or major accidents, and the exercises for biological terrorism can build on these experiences. However, industrial disasters like the ones in Seweso (1976) or Bhopal (1984) or the recent outbreak of Severe Acute Respiratory Syndrome (SARS) suggest the need to develop and test the emergency procedures at all levels. Many lessons can also be learned from the terrorist strikes against the Twin Towers in New York on 11 September 2001.

In Europe, with its many small countries, a need exists to run cross-border training exercises whereby the organization of emergency response procedures among EU members is tested and improved (e.g., by discovering and resolving legal and bureaucratic obstacles preventing emergency and law enforcement or specialized military units to operate on the territory of another EU member). Similarly, the EU-wide technical assistance programs mentioned above must be tested in practice.

The important point to bear in mind is that the preparation and finetuning of procedures takes

many years, and these activities should be undertaken sooner rather than later.

What are the WHO recommendations?

The attacks of 11 September 2001 and the delivery of anthrax spores through the mail shortly afterwards considerably magnified the threat perceptions regarding biological terrorism. The effects were not limited to the United States: the many reports of anthrax attack hoaxes in other countries increased threat awareness across the world. As a direct consequence, the WHO updated its guidance with regard to smallpox and expanded the smallpox section of its website with advice and background information (URL <<http://www.who.int/csr/disease/smallpox/en/>>). On 26 October 2001, Director-General Gro Harlem Brundtland announced the conclusion in a press statement:

“Existing vaccines have proven efficacy but also have a high incidence of adverse side-effects. The risk of adverse events is sufficiently high that mass vaccination is not warranted if there is no or little real risk of exposure. Individual countries that have reason to believe that their people face an increased risk of smallpox because of deliberate use of the virus are considering options for increasing their access to vaccines. The vaccines would be given to people who are at risk of exposure to smallpox, including health and civil workers, and would be used in a search and containment exercise should an outbreak occur.”

The WHO thus recommended against the vaccination of entire populations or large groups of emergency personnel because of the relatively low risk of an outbreak and the possibility of adverse health effects of the vaccine. Only those people who are suspected of actually having been exposed to the disease should receive the vaccine, or individuals working with pox viruses (including smallpox and monkey pox). It also confirmed its proved strategy of ‘search and containment’, which involves the identification and vaccination of people with smallpox and those who have been in contact with infected people. At the same time, the WHO advises governments with respect to the quality of the vaccine inventories and the possible need to increase stocks of vaccine for use in the event of an outbreak.

Following the WHO updating its guidance, many countries have undertaken reviews of their smallpox vaccine inventories and their measures to respond to a possible outbreak.

Meanwhile the destruction of the last inventories of smallpox strains in the two WHO-designated repositories, namely the Centers for Disease Control

and Prevention (CDC) in Atlanta, Georgia (USA) and the State Research Centre of Virology and Biotechnology in Koltsovo, Russia, has been postponed in order to allow further research into the virus and new generations of vaccine. This confirmed a decision already reached in December 1999.

The WHO also participates in many interregional and global initiatives to prevent or manage smallpox outbreaks.

Which measures is the European Union currently undertaking?

Especially since the terrorist attacks of 11 September 2001 and the subsequent mailing of anthrax spores in the USA, the European Union (EU) is taking a number of steps in the sphere of health security to improve its preparedness and response capabilities with regard to biological and chemical agent attacks. In particular, it has set up a rapid alert system-biological chemical attack (RAS-BICHAT), which became operational in June 2002 and functions 24 hours a day, seven days a week. The EU has reviewed lists of pathogens and developed a matrix for prioritizing public health actions. Furthermore, a platform of cooperation has been set up between public health laboratories in the EU member states, and a network of high safety laboratories was created.

Smallpox is included in this list of reviewed pathogens. The Health Security Committee (which was set up by the EU Commission in October 2001 to expedite the development of laws and regulations) also prepared case definitions for surveillance purposes (which will eventually become mandatory for all EU members) and clinical guidelines. In addition, the EU Commission organized the sharing of information on smallpox emergency plans, and made comparative analyses of the respective measures and alert levels. At the request of the EU Commission in November 2001, the European Medicines Evaluation Agency (EMA) created two expert groups, one of which was to develop specific recommendations and guidance regarding vaccines, in particular those against smallpox. It has published draft guidance on the development of vaccines against smallpox, including second-generation vaccines in June 2002. In July 2003, the EU Commission - partly prompted by the outbreak of SARS - adopted a proposal to create a European Centre for Disease Prevention and Control.

On 7 November 2001 the EU Commission, the G-7 countries and Mexico agreed on the Global Health Security Action initiative in Ottawa; other meetings have taken place or are planned. The initiative

seeks to promote cooperation on smallpox emergency plans and training, laboratory detection techniques, risk management and communication, and patient isolation techniques, among other things. At the end of 2002 an exercise based on a smallpox outbreak was organized to test communication channels and evaluate existing emergency plans. Other tests and exercises are being planned. The WHO is fully associated in these activities, and participants at the meeting of 6 December 2002 have agreed to replenish the WHO smallpox vaccine stocks, and to organize a multi-national exercise in 2003 to test the reaction to smallpox contamination and the development of cooperation between the high-security laboratories of the participating countries. The EU, both through the Health Ministers of the member states and the Commission, participate in inter-regional and global programs to share surveillance data on possible outbreaks of contagious diseases.

From November 2001 onwards the EU Commission entered in discussions with the European Pharmaceutical industry, and set up a joint task force to evaluate the availability and production, storage, and distribution capacity for vaccines and medicines in the event of a biological attack.

Despite the range of efforts to coordinate preparedness and response on the EU level, some EU members continue to resist the creation of an EU-level stockpile of any medicine or are uninterested in the creation of an EU consortium to procure vaccines or other medicines. Most EU members still have first generation vaccines against smallpox, but despite the assessment that these vaccines do meet present day quality standards, they do not plan on buying second generation vaccines when they become available. In line with the advice issued by the WHO, EU members have confirmed the existence of a national 'search and contain' or ring vaccination strategy. Several EU members have meanwhile replenished their smallpox vaccine stocks.

The EU has made progress in terms of preparedness and response in the case of a major outbreak of infectious diseases (including smallpox), but the member states still face several important questions regarding the degree of EU integration of health security that they are willing to accept. The EU has also kept the candidate states that are joining the EU in 2004 informed of the relevant measures, but steps still need to be taken so that the new members meet the overall EU standards in the shortest possible time frame. There are also ongoing discussions regarding the wisdom of pre-emptive mass vaccinations against smallpox (as in the USA).

Should we be concerned?

Over the past decade there is a perception of an increased CBW threat. The threat of terrorists resorting to biological and chemical agents confronts policy makers with many imponderables. The identity and the motives of the terrorists can differ widely; the perpetrators have a broad range of targets (humans, animals, the food chain, the environment, and so on) and instruments (in terms of human, animal and plant pathogens, and toxic substances) to cause casualties or economic and societal disruption. Such attacks have been extremely rare in the past, so history offers little guidance as to what the future may hold.

The fear of a deliberate release of the smallpox virus has been prompted by a combination of factors, including the revelations about an alleged Soviet smallpox weaponization program after the global eradication of the disease and the concern that former Soviet scientists may have been lured to other countries to work on similar programs, the terrorist attacks on 11 September 2001, the mail-delivered anthrax spores in the United States in the same month, and the rapid spread of SARS.

However, there is no concrete public evidence to suggest that there exist undeclared holdings of smallpox outside the official WHO-designated repositories in the United States and Russia.

Nevertheless, a future outbreak of smallpox - whether accidental or deliberate - cannot be fully excluded. The spread of the virus in an increasingly immunologically naive population could wreak havoc in the affected societies. Therefore it is wise for governments and public authorities to take relevant preventive measures without resorting to mass mobilization of national resources as if the country is waging total war. Most of these measures can be generic and cost-effective. Moreover, they are no dead investments. Society as a whole will benefit greatly from improvements in the health and emergency infrastructure and emergency procedures. However, it is important for the governments and public authorities to realize that counter - and preventive measures must be taken before an outbreak occurs, and that such preparations take several years before achieving maximal effectiveness. Here is a clear and present responsibility of parliaments and governments.

Available online at www.sciencedirect.com

